PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SUVN-951-02		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN 03/00393	16.12.2003	18.12.2002
International Patent Classification (IPC) or both national classification and IPC		
C07D513/04		
Applicant		
SUVEN LIFE SCIENCES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.07.2004	14.03.2005
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00393

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-4, 6-48	as originally filed
5	filed with telefax on 23.02.2005

Claims, Numbers

1-8, 9 (part), 10 (part), 11-17	as originally filed
9 (part), 10 (part)	filed with telefax on 23.02.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-17

because:

☒ the said international application, or the said claims Nos. 11-17 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

POINT III.

For the assessment of the presently worded claims 11 to 17 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a new medical treatment.

POINT V.

The following documents , quoted in the I.S.R., have been considered as relevant for the examination of the present application . Their numbering will be adhered to for the rest of the procedure.

(1) J.O.C., vol. 529, no. 1, 1997, pages 445-453.
(2) Database CA [Online] C.A., XP002274554 retrieved from STN Database accession no. 139:6769 & CN 1345724 (24.04.2002)
(3) WO-A-02/42292.
(4) WO-A-00/34242.
(5) GB-A-2 341 549.

1. Novelty.

In view of the exclusion of the scope of present claim 9 of the byproduct 9 of page 451 , RH column, of (1) , all the claims are novel with respect to the content of document (1). Additionally , the contents of (2)-(5) do not affect the novelty of the claims , since the pharmacologically active compounds disclosed therein do not fall within the scope of the claimed matter on file.

2. Inventiveness.

In view of the contents of the documents quoted above , the claimed matter can be regarded as inventive , because the pharmacologically active compounds of present application are not

suggested in those documents.

3. Formal Point.

3.1 The description should be adapted to present reformulation of claim 9 when the application will reach the European regional proceedings.

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European Patent Publication 457,701 refers to aryloxy amine derivatives as having high affinity for 5-HT_{1D} serotonin receptors. These compounds are said to be useful for treating diseases related to serotonin receptor dysfunction, for example, migraine.

European Patent Publication 497,512 A2, refers to a class of imidazole, triazole and tetrazole derivatives that are selective agonists for "5-HT_1-like" receptors. These compounds are said to be useful for treating migraine and associated disorders.

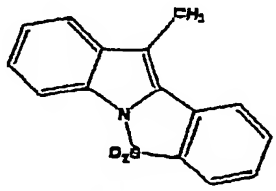
International Patent Publication WO 93/00088 describes a series of tetrahydrocarbazole derivatives, as 5-HT_1 receptor agonists, useful for the treatment of migraine and related conditions.

International Patent Publication WO 93/23398, refers to fused imidazole and triazole derivatives as 5-HT_1 receptor agonists, for the treatment of migraine and other disorders.

Schoeffter P. et al. refers to methyl 4-{4-[4-(1,1,3-trioxo-2H-1,2-benzoisothiazol-2-yl)butyl]-1-piperazinyl}1H-indole-3-carboxylate as a selective antagonist for the 5-HT_{1A} receptor in their paper "SDZ216-525, a selective and potent 5-HT_{1A} receptor antagonist", European Journal of Pharmacology, 244, 251-257 (1993).

International Patent Publication WO 94/06769, refers to 2-substituted-4-piperazine-benzothiophene derivatives that are serotonin 5-HT_{1A} and 5-HT_{1D} receptor agents useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

Tiziana Benincori et al has described in a research article (Journal of Organometallic Chemistry, 529 (1997), 445 – 453), a tetracyclic indole derivative, 1H-indole[1,2-b]benzo(d)isothiazole-10-methyl-5,5'-dioxide (see structure below, Benincori et al, Compound 9, as referred in above citation).



Benincori et al; Compound 9

The authors synthesized the above compound accidentally and it was obtained as an impurity during the synthesis of some dimeric indole ligands; as a part of development of chiral anisotropic biheteroaromatic diphosphines. However, authors have not mentioned any application with regard to the above compound.

Summary of the Invention:

The present invention relates to compounds of general formula (I), its stereoisomers, its radioisotopes, its N-oxide, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, its useful bio-active metabolites and any suitable combination of the above.

The compounds of general formula (I) are as follows:

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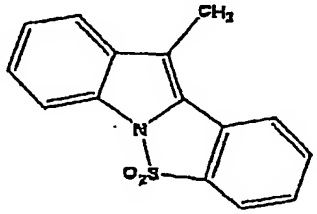
R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, perhaloalkoxy, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_8 and R_7 or R_7 and R_8 or R_8 and R_9 together with carbon atoms to which they are attached may form a five or a six membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or optionally R_{11} and R_{12} together with the carbon atoms to which they are attached may form a three to six membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or optionally either R_{11} or R_{12} are such substituents which may allow formation of bond with either R_{16} or R_{17} to form a 5, 6 or 7–membered heterocyclic ring; and its stereoisomers and its salts, with a proviso that R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9 and X are all not Hydrogens so that 1H-indole[1,2-b]benzo(d)isothiazole-10-methyl-5,5'-dioxide for the Formula indicated below



is excluded from said compound of Formula III.

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10. A process provided for the preparation of novel intermediate of the general formula (III), according to any one of the routes which comprises of,

Route 1 : cyclizing a compound of formula (V) given below,